

We claim:

1. A humanized immunoglobulin which binds to human von Willebrand factor.
2. The immunoglobulin of claim 1 which competes with mouse antibody AJvW-2 for specific binding to von Willebrand factor.
3. The immunoglobulin of claim 1 which is an antibody comprising a heavy chain variable region shown in Figure 2a (SEQ. ID. NO. 3) and a light chain variable region shown in Figure 2b (SEQ. ID. NO. 4).
4. A humanized immunoglobulin that is a humanized form of mouse antibody AJvW-2.
5. The humanized immunoglobulin of claim 1, comprising complementarity determining regions from the mouse AJvW-2 antibody, and heavy and light chain variable region frameworks from human I3R antibody heavy and light chain frameworks, provided that at least one position selected from the group consisting of LC-48, LC-70, LC-71, HC-28, HC-48, HC-49 and HC-67 is occupied by the amino acid present in the equivalent position of the mouse AJvW-2 antibody heavy or light chain variable region framework, which humanized antibody specifically binds to vWF with an affinity constant between 10^7 M^{-1} and ten-fold the affinity of the mouse AJvW-2 antibody.
6. The humanized immunoglobulin of claim 5, which is an antibody wherein each position selected from the group consisting of LC-48, LC-70, LC-71, HC-28, HC-48, HC-49 and HC-67 is occupied by the amino acid present in the equivalent position of the mouse AJvW-2 antibody heavy or light chain variable region framework.
7. The humanized antibody of claim 6, wherein at least one position selected from the LC-62, LC-73, LC-83, HC-1, HC-78 and HC-118 is occupied by an amino acid present in the equivalent position of a human antibody heavy or light chain consensus sequence.
8. The humanized immunoglobulin of claim 5 comprising a heavy chain variable

region shown in Figure 2a (SEQ. ID. NO. 3) and a light chain variable region shown in Figure 2b (SEQ. ID. NO. 4), wherein one or more amino acid positions may be substituted by alternatives as shown in Tables 1 and 2.

9. The humanized immunoglobulin of claim 1, comprising a humanized heavy chain having at least 85% identity with the humanized heavy chain shown in Figure 2a (SEQ. ID. NO. 3) and a humanized light chain having at least 85% sequence identity with the humanized light chain showing in Figure 2b (SEQ. ID. NO. 4), provided that at least one position selected from the group consisting of LC-48, LC-70, LC-71, HC-28, HC-48, HC-49 and HC-67 is occupied by the amino acid present in the equivalent position of the mouse AJvW-2 antibody heavy or light chain variable region framework.

10. The immunoglobulin of claim 1, comprising two pairs of light/heavy chain dimers, wherein each chain comprises a variable region and a constant region.

11. The immunoglobulin of claim 1, which is a Fab fragment or a $F(ab')_2$.

12. The humanized immunoglobulin of claim 1 having complementarity determining regions (CDRs) from AJvW-2 and heavy and light chain variable region frameworks wherein the sequence of the heavy chain variable region framework is a consensus sequence of human immunoglobulin heavy chain variable region frameworks.

13. The humanized immunoglobulin of claim 1, which has an IgG₂ or IgG₄ immunoglobulin subtype.

14. The humanized immunoglobulin of claim 1, wherein the constant region is a C γ 2 C γ 4 region.

15. A method of producing an immunoglobulin comprising: culturing a cell line that encodes heavy and light chain chains of a humanized immunoglobulin, whereby a humanized antibody which competes with mouse antibody AJvW-2 is expressed; and

recovering said humanized antibody.

16. The method of claim 15, further comprising formulating the humanized antibody with a pharmaceutically acceptable carrier to produce a pharmaceutical composition.

17. A pharmaceutical composition comprising: a humanized immunoglobulin which competes with mouse antibody AJvW-2 for specific binding to von Willebrand factor, and a pharmaceutically acceptable carrier.

Sub B1
18. A method of treating a patient having or at risk of a thrombotic disease or athelosclerosis, comprising: administering to said patient an effective dose of a humanized immunoglobulin which competes with mouse antibody AJvW-2 for specific binding to von Willebrand factor.

19. The method of claim 18, wherein the immunoglobulin is a humanized form of mouse antibody AJvW-2.

20. The method of claim 18, wherein the immunoglobulin comprises a heavy chain variable region shown in Figure 2a (SEQ. ID. NO. 3) and a light chain variable region shown in Figure 2b (SEQ. ID. NO. 4).

Sub B2
21. The method according to claims 18-20, wherein the treatment is for stroke, transient ischemic attack, unstable angina, acute myocardial infarction, angina pectoris, peripheral vascular disease, deep vein thrombosis, hemolytic uremic syndrome, hemolytic anemia, acute renal failure, thrombotic thrombocytopenic purpura, ischemic complications caused by acute and subacute thrombosis or restenosis after endovascular intervention or preventing ischemic complications caused by reocclusion after thrombolytic treatment in acute myocardial infarction as an adjunctive therapy.

R-126
22
21. A cell line that produces a human immunoglobulin which competes with mouse antibody AJvW-2 for specific binding to von Willebrand factor.